

Hemorrhagic Cholecystitis.

Report of a case with comprehensive literature review and treatment algorithm



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Haemorrhagic cholecystitis. Report of a case with comprehensive literature review and treatment algorithm

Hemorrhagic Cholecystitis is a rare condition and usually represents a complication of acute cholecystitis. The clinical presentation is quite overlapping and usually involves abdominal pain that may be associated with fever, jaundice, nausea, vomiting, and finally haemobilia. It frequently involves patients with preexisting conditions such as chronic kidney disease undergoing hemodialysis or anticoagulation therapy. Due to the deadly potential of this condition attention must be high during diagnostics and treatment in order to avoid an ill-fated conclusion. To our knowledge, there is a lack of a comprehensive review on the subject as most of the literature consists of case reports or small case series. In order to give a contribution to improving the treatment strategy of this condition, we report a case successfully treated with cholecystectomy, and performed a literature review. Using the term "Hemorrhagic Cholecystitis", on PubMed database we found 67 cases reported in the English literature. The cases were analyzed by two researchers and clinical information was extrapolated and organized, aiming to create a comprehensive review on the subject, that may be clear and useful in clinical practice.

KEY WORDS: Hemorrhagic cholecystitis, Surgical treatment

Introduction

Hemorrhagic Cholecystitis (HC) is a rare and potentially life-threatening condition. The first report using the term of HC is in the Spanish language by Wybert A. et al in 1946¹, but there are earlier reports of haemobilia and rupture of the gallbladder with hemoperitoneum that may be conducted to HC². It is defined as a complication of severe acute cholecystitis (AC) with the erosion of the gallbladder mucosa due to inflammation and

bleeding into the gallbladder lumen. More recently there was a report of hemorrhagic cholecystitis in metachromatic leukodystrophy. It is reported to occur in up to 12% of AC³. It is frequently associated with preexisting pathologies, such as liver and kidney disease and anticoagulation therapy. Aside from symptoms similar to AC or Cholangitis, HC may present hematemesis and melena, originating from haemobilia, with a subsequent drop in hemoglobin followed by hemorrhagic shock. During diagnostics, ultrasound, computer tomography (CT), magnetic resonance imaging (MRI), Endoscopic Retrograde Cholangiopancreatography (ERCP), and angiography may all be utilized. The treatment options range from angiographic embolization and ERCP to cholecystectomy, open or laparoscopic. In bad surgical candidates, Cholecystostomy is a bridging-to-surgery option. To our knowledge, no comprehensive review on HC is present in the literature which is mainly represented by case reports and a case series of patients undergoing ultrasonographic evaluation. Herein, we conducted an extensive review of the English literature aiming to create a comprehensive review on the subject, clear and useful in clinical practice.

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Case Report

A fifty-eight-year-old male patient was admitted to the emergency department for upper right quadrant abdominal pain lasting more than 72 h. Medical history was significant for poliomyelitis and hypertension treated with ramipril and amlodipine. On examination, he was hemodynamically stable. The abdomen was tender in the upper right quadrant, and a slightly positive Murphy sign was present. Initial laboratory results showed hemoglobin 13.7 g/dl, leukocytosis was 24.64 103/ μ L, CRP was 14.4 mg/dl, and procalcitonin 1,68 ng/ml, total and direct bilirubin were 1.55mg/dl and 0.47mg/dl respectively. Abdominal contrast-enhanced computer tomography (CT) was performed, showing a distended gallbladder with a diffusely and slightly thickened wall, intraluminal, perihepatic and suprahepatic hyperdense fluid collection, and active bleeding around the infundibulum of the gallbladder (Fig. 1). Sludge was present in the gallbladder and in the biliary duct, which was slightly dilated, showing the presence of an air bubble. A diagnosis of cholecystitis with concomitant cholangitis was made, and the patient was put on an IV fluid and piperacillin/tazobactam therapy and hospitalized in a general surgery ward. On hospitalization day (HD) four, Magnetic Resonance Cholangiopancreatography (MRCP) was performed, showing gallbladder stones and stenosis of the terminal portion of the bile duct without proximal dilation. Laboratory confirmed the absence of cholestasis. A hepatic sub-capsular collection was also noted on the gallbladder bed.

On HD six, the patient was ready for discharge when he developed a sudden relapse of right upper quadrant abdominal pain. A new contrast-enhanced abdominal CT was performed, showing a worsening of distension, wall thickening, and gallbladder perforation. Hyperdense material suggestive of blood clots was found inside and outside the gallbladder in a perihepatic collection. Active bleeding was noted at the gallbladder infundibulum.

Urgent laparoscopic exploration revealed hemo- and chole-peritoneum and tenacious adhesions of the trans-

verse colon with liver and in the subdiaphragmatic space. The procedure was converted to a bilateral subcostal incision. Adhesion takedown revealed a large, distended, perforated, and gangrenous gallbladder filled with blood clots. Cholecystectomy was performed, and histology confirmed gangrenous hemorrhagic cholecystitis. The postoperative course was uneventful, and the patient was discharged on postoperative day

LITERATURE REVIEW

The Pubmed database was queried for the keywords "hemorrhagic cholecystitis" yielding more than 3000 results. Relevant English language titles were selected, and the abstracts were analyzed by two researchers. Furthermore, all selected manuscripts' bibliography was further scrutinized for missed cases. Fifty-four publications were found compatible, and the full text was analyzed, finding 67 cases (Table I) responding to the characteristics of HC. All the cases were inspected, and clinical information was extracted and organized. Ultimately, to fill the gap in the literature, a manuscript was composed to give a complete guide of the clinical presentation, diagnostics, differential diagnosis, and treatment. A table of cases and a treatment algorithm is proposed.

CLINICAL PRESENTATION

HC is a rare condition bearing a morbidity rate of 32% to 58% and a mortality rate of 15% to 20%⁴. It is usually a complication of acute cholecystitis. Analysis of the available English literature consists mainly of case reports, revealed 67 reported cases of HC. A critical review of our case and the 67 cases reported in the literature delineates some potential risk factors for the development of HC. In particular, anticoagulation therapy is present in 77% of the patients, chronic kidney disease (CKD) in 33%, 40% had a cardiac disease of any kind in 40%, cirrhosis in 17%. Finally, in 63% of

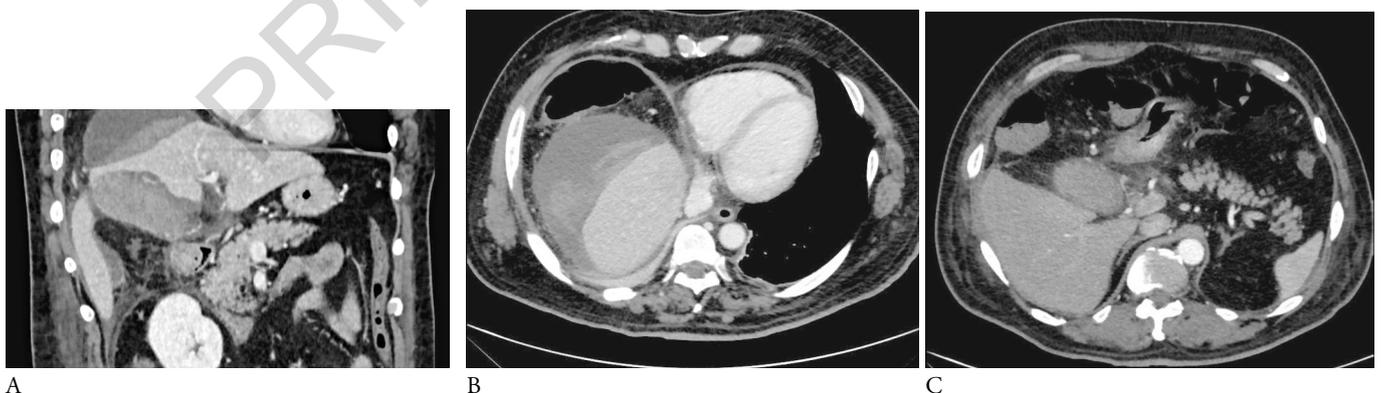


Fig. 1: Hemorrhagic cholecystitis with intraluminal and perihepatic hyperdense fluid collection (A), suprahepatic collection with hyperdense material (B) and active bleeding around the infundibulum of the gallbladder (C).

patients 3 or more preexisting medical conditions are reported. Shope et al. reported one case of HC following a motor vehicle accident in a young female patient with no comorbidities⁵. The most common symptom is pain usually located, but not limited to, the right upper quadrant. Fever, nausea, and emesis are frequently associated. Some cases may present with jaundice and signs of gastrointestinal bleeding, ranging from a positive occult blood test to frank melena or hematemesis. The patients should be evaluated for hemodynamic stability because hemorrhagic shock may ensue if heavy bleeding occurs. Moreover, worsening of abdominal pain may indicate perforation of the gallbladder, which in this scenario may lead to hemoperitoneum. Tenderness, positive Murphy sign, and rebound are characteristic and may be associated with jaundice and a palpable mass in the right upper quadrant. Laboratory may indicate alteration of blood cell count with anemia and leukocytosis. Serum transaminase and cholestasis tests may be altered as well as amylase and lipase. It is useful to check for alteration of the coagulation tests, mainly in patients under anticoagulant treatment, affected by chronic kidney disease (CKD) and cirrhosis. The presence of compromised clinical conditions and multiple comorbidities may necessitate a multidisciplinary approach.

Because clinically related aspects of HC lack of specificity, imaging has a crucial role in the diagnosis of HC. In most reported cases, the patients were evaluated by one or more imaging techniques before the diagnosis was confirmed. Ultrasound sonography plays an important role and is reported in many cases as the first diagnostic approach or as a confirmation after a CT scan. Chinn et al. reported the ultrasonographic characteristics of 19 patients affected by HC, 84% had lithiasis, whereas in 14 patients they reported unusual sonographic features such as focal gallbladder wall irregularity, intraluminal membranes, and coarse non-shadowing non-layering intraluminal echoes⁶. In 1983, Jenkins et al. described the sonographic appearance of blood in the gallbladder as clumps of echogenic material. The echogenicity is analogous to that of bile mixed with pus or clumped thick sludge found in the cystic duct or common-bile-duct obstruction. Furthermore, if the echogenic material remains suspended, differential diagnosis with carcinoma may be difficult. Moreover, blood clots can undergo rapid transformation, progressing from an initial solid appearance into a mixed one, and, finally, into a cystic appearance following lysis and melting⁷. Finally, as highlighted by Reens, ultrasound may be a valid diagnostic tool at the bedside in the emergency department for a rapid planning of further management⁸. The angiographic “pseudo-vein sign” which describes contrast extravasating into a hollow organ was reproduced on Doppler sonography in a case reported by Gremmels et al. The ultrasound imaging showed a pulsatile flow suggesting the presence of a vessel and the diagnosis of a gallbladder tumor. At surgery, no neoplasm was found

and this finding was defined as a sonographic “pseudo-artery” sign⁹. A contrast-enhanced CT scan can frequently confirm the diagnosis of HC. Blood within the gallbladder may appear as a high-density fluid with or without layering that can mimic sludge¹⁰. As with ultrasonography, in some cases, it can appear as vascularized soft tissue-mimicking a tumor⁹. Irregularity of the gallbladder wall with hyperdense material inside and outside the gallbladder can be seen in cases of hemoperitoneum caused by perforation of the gallbladder¹¹. Arterial phase-contrast enhancement may clarify the diagnosis, by showing active bleeding, if present, but may also lead to the wrong interpretation of a blood vessel in the context of a soft tissue mass^{9,10,12}. MRI is useful whenever either cholestasis or a tumor is suspected. In cases of jaundice, Magnetic Resonance Cholangiogram (MRCP) is a gold standard technique of imaging to investigate obstruction of the bile duct. It may reveal cholecystolithiasis and choledocholithiasis as well as hematic content of the gallbladder and the duct. Blood usually appears as high or mixed signal intensity on T1-weighted images which remains high or mixed intensity in the contrast-enhanced scan. T2-weighted imaging is predominantly low. These MRI characteristics may be useful to exclude the neoplasm of the gallbladder¹³⁻¹⁵. Endoscopic Retrograde Cholangiogram (ERCP) is useful in cases of obstruction and may show haemobilia in around 30% of cases with HC^{16,17}. The multiple aspects of blood in the gallbladder, at different imaging modalities, underscores the frequent difficulty of diagnosis even at multiple imaging methods. Hence, knowledge and awareness of the condition by the radiologist are of paramount importance.

DIFFERENTIAL DIAGNOSIS

When considering the diagnosis of HC, several conditions need to be excluded. The main ones are AC, haemobilia, Cystic Artery Pseudoaneurysm (CAPsA), gallbladder wall hematoma, and gallbladder tumor. Being its precursor, AC bears a lot of similarities with HC. Under a clinical point of view, the main difference lies in the potential drop of hemoglobin, which in severe cases, will lead to hemodynamic instability and hemorrhagic shock. Luckily, the differentiation between AC and HC in most cases is possible due to the imaging studies mentioned above. Rupture of a CAPsA with active bleeding may be associated with HC or may appear without any sign of cholecystitis or frank haemobilia, hence, it may be considered a different pathologic entity. Moreover, its treatment is mainly via interventional radiology and may be associated with a cholecystectomy when inflammation is present¹⁸.

Nguyen et al, have described 2 cases of acute cholecystitis associated with PsA. The authors sustain that the disruption of the vessel wall leads to the formation of

Author	Year of publication	Patient age/sex	Anticoagulation	CKD	Cirrhosis	> 3 comorbidities	US	CT	MRI	ERCP	Angiography	Cholecystostomy	Lap choly (+* = converted)	Open choly
Khoury et al.	2019	43 f	-	-	-	+	+	-	-	-	-	-	+	-
Garcia-Perez et al.	2011	24 f	+	-	-	-	+	-	-	-	-	-	+*	-
Chul Kim et al.	2007	55 m	-	-	+	-	+	+	-	-	-	+	-	-
Gremmels et al.	2004	66 m	-	-	-	-	+	+	-	-	-	-	-	+
Donn et al.	2018	63 m	+	-	-	-	+	+	-	-	-	+	+*	-
Sweeny et al.	2019	78 m	+	-	-	+	+	+	-	+	-	-	+	-
Shishida et al.	2017	79 m	+	+	-	+	-	+	+	+	-	-	+	-
Parekh et al.	2010	60 m 50 m	- -	- -	- -	+	+	-	+	+	-	-	+	-
Chin et al	1987	50 f 53 f 44 f 32 m 39 f 67 m 74 m 65 m 44 m 44 m 78 f 49 m 34 f 69 m 72 m 59 f 53 m 73 m 63 m					+							
Lauria et al.	2019	73 m	+	+	+	+	+	+	-	-	-	-	-	+
Hancock et al.	2008	49 f						+						+
Karsumichi et al.	2002	68 m		+			+					+	-	+
Jenkins et al.	1983	65 m					+	+						+
Kwon et al.	2012	75 m	+					+		+			+	
Lai et al.	2009	81 m		+		+	+	+				+		+
Morris et al.	2008	91 f	+					+						+
Pandya et al.	2008	85 f	+				+	+				+		
Reens et al.	2019	76 m	+			+	+	+				+		
Seok et al.	2013	84 m						+					+	
Shope et al.	2004	35 f						+					+	
Tavernaraki et al.	2011	64 m	+	+		+		+						+
Wagner et al.	1985	39 m												+
Yiu-Chiu et al.	1980	45 m			+		+	+						
Vettoretto	2001	17 m					+	+			+			+
Stempel	1993		+									+		
Moskos	1991													

(segue)

Author	Year of publication	Patient age/sex	Anticoagulation	CKD	Cirrhosis	> 3 comorbidities	US	CT	MRI	ERCP	Angiography	Cholecystostomy	Lap choly (+* = converted)	Open choly
Rajman	1989													
McFadden	1987			+										+
Brady	1985													
Butterfield	1971				+									
Hess	1964													
Michelini	1962													
Gallarate	1962													
Shakharuk	2021	55 m	+	+		+	+	+					+	
Zhang	2020	57 f	+				+	+	+	+			+	
Hasegawa	2021	70 m	+	+		+	+	+		+			+	
Cirillo	2020	79 m	+					+						+
Pickell	2020	67 m		+		+		+					+	
Shah	2020	66 m			+	+		+					+	
Chen	2020	63 f						+	+	+				+
Chen	2010	75 f	+				+	+				+	+	
Yam	2020	51 f		+		+	+	+			+	+		+
Leaning	2021	73 m	+	+		+	+	+	+				+	
Rahesh	2020	f					+	+					+	
Tarazi	2019	87 m	+			+		+				+		
Tarazi	2019	65 f	+			+	+	+						+
Tarazi et al.	2019	92 f				+	+	+				+		
Kinnear	2017	74 m	+			+	+	+						+

a pseudoaneurysm. This appears to occur most commonly with gallstones impacted in the gallbladder neck with the erosion of the adjacent cystic artery¹⁹. On the other hand, Kumar et al agree that, in addition to inflammation in the hepatobiliary and pancreatic system, CAPsA may be iatrogenic and develop secondary to liver biopsy, laparoscopic cholecystectomy, ERCP, and liver transplant or may be caused by trauma, malignancy, and arteriovenous malformations²⁰. Whatever its pathogenesis, most of the reviewed cases of HC did not have evidence of a PsA on imaging. The connection between CAPsA and HC must be further investigated in order to define the pathogenesis. Intramural Gallbladder Hematoma (IGH) is a hematoma of the cholecystic wall. It commonly occurs after trauma including percutaneous liver biopsy and is associated with gallbladder neoplasm, aneurysm rupture, coagulation disorders, renal impairment, and hepatic cirrhosis. Its clinical manifestation and risk factors are interlocking, but it is rarely associated with cholecystitis. Moreover, the bleeding is confined to the wall and leaves the lumen free of blood²¹. Haemobilia is a manifestation common to various conditions affecting the biliary system. The most common causes of haemobilia are iatrogenic, traumatic, and neoplastic, and

only about 6% of them is due to inflammation²². It has been reported that around 30% of the patients suffering from HC may manifest haemobilia so other causes of haemobilia must be excluded when evaluating a patient with haemobilia and suspected HC. Finally, gallbladder tumors may manifest themselves with haemobilia and may show similarity to HC on imaging investigation. Several cases were reported in the literature presenting with soft tissue within the gallbladder lumen, mimicking a tumor during diagnostics but consisting only of a blood clot at pathological examination^{9,14}. Differentiation of the above-reported entities is crucial for the treatment choices.

TREATMENT

Several treatment strategies are reported in the literature ranging from a conservative approach up to surgical exploration. Tarazi et al reported a case of HC treated conservatively with antibiotic therapy. The patient was first diagnosed with acute appendicitis and started on antibiotic therapy. Subsequently, abdomen contrast-enhanced CT revealed active bleeding in the gallbladder.

The patient was treated conservatively, discharged after 5 days, and underwent elective laparoscopic cholecystectomy²³. Cholecystostomy is considered a “bridging to surgery” procedure in cases of AC in bad surgical candidates. The technique consists in positioning a percutaneous transhepatic 7Fr drainage catheter in the gallbladder lumen under ultrasound guidance. This procedure was reported in 11 cases of whom only 5 underwent a subsequent cholecystectomy: 5 patients were treated conservatively, and one patient died due to multiple comorbidities. In most cases, blood, dark or fresh, and eventually mixed with bile, was found in the gallbladder lumen. One case describes a solid clot with no discharge from the drain^{8,12,23-25}. ERCP was already discussed in the diagnostics section. As far as treatment goes, ERCP’s main contribution is in cases of jaundice, when gallstones or blood cause obstruction of the common bile duct. Removing the obstruction leads to normalization of the bile flow, reduction of pain, and resolution of jaundice¹⁶. During the procedure, endoscopic naso-biliary drainage (ENBD) tube can be left in place in order to maintain decompression and monitor bleeding¹³. That said, ERCP is one of the major causes of haemobilia and its use must be limited to the above-reported cases²². Angiography is useful in cases of active bleeding found at CT scan or in cases of HC with CAPsA. During the procedure, the celiac trunk and common hepatic artery are catheterized, and the cystic artery is reached, studied, and eventually embolized. Some cases reported the origin of the hepatic artery from the superior mesenteric artery. In case of active bleeding during HC in a bad surgical candidate, angiography with transcatheter embolization is a valid choice that may give the possibility to stabilize the patient for surgery²⁵. HC, as mentioned earlier and reported by Nguyen et al, may be associated with CAPsA. In such cases, angiography may be useful for active bleeding control or in order to exclude the PsA, securing the subsequent cholecystectomy¹⁹.

Laparoscopic cholecystectomy is one of the most common general surgery procedures performed. However, all surgeons are aware that in cases of severe inflammation this common procedure may become technically challenging and insidious. Conversion rates depend on multiple factors and vary widely in the literature (1.8-27.7%)²⁶. Cholecystectomy is indicated in most HC cases. The decision for intervention and the right timing depends on whether the patient is a good surgical candidate, on the severity of the inflammation, and hemodynamic instability due to bleeding. Even more, the availability of angiography and ERCP in the institution may influence both, the timing, and the surgical approach. Therefore, cholecystectomy may be performed immediately or be delayed, after bleeding and inflammation control. Forty patients among 68 cases reported in the literature (58%) underwent a cholecystectomy. Twenty-one cases were approached laparoscopically of whom, 6 pro-

cedures were converted (28.6%). The remaining 28 cases were approached with an open technique. Only 2 cases were treated with a delayed cholecystectomy, thus suggesting the possibility of a conservative treatment in selected cases. The high rate of conversion from laparoscopy to open surgery and the low rate of conservative treatment with a delayed elective cholecystectomy may imply the particular severity of HC. During such technically challenging cholecystectomies, either open or laparoscopic, the surgeon must assess for active bleeding, and obtain the Critical View of Safety (CVS) to preserve the extrahepatic bile structures. Near-infrared fluorescent cholangiography (NIFC) with intravenous indocyanine green (ICG) injection before surgery is an emerging tool for the intraoperative study of the extrahepatic bile ducts’ anatomy. It was reported that compared to wight light, NIFC enhances the visualization of the extrahepatic bile duct anatomy and may reduce the rate of bile duct lesions²⁷. Technology is available for the laparoscopic and the laparotomic approach. The reports of time of preoperative administration of ICG vary widely. Dip et al, suggest that in accordance with the literature, the currently recommended time of dye administration for optimal anatomy visualization is 45 minutes before surgical incision. The administration further away from the procedure may give better visualization but may reveal not practical in an emergency setting. Reports of administration immediately before the incision are present but, this timing may impair the efficacy of the technique²⁸. Clearly, to get the best out of the technique, some sort of preoperative planning is necessary precluding the use of NIFC in hemodynamically unstable patients. In especially complex cases, when CVS cannot be obtained, partial cholecystectomy may be the better choice to avoid the main biliary duct lesion²⁹. Postoperatively, the reported results depend on the severity of the preoperative conditions. In two cases, mortality was reported which seems to be significantly lower considering the previously reported mortality rate of 15-20%⁴. The reason for this discrepancy is not clear. Bleeding with postoperative anemia, pneumonia and a biliary leak were the other reported complications. The average length of stay (LOS) after surgery was 12.2 days which is much longer than the standard LOS after a cholecystectomy. These data highlight the complexity of the treatment of these potentially dangerous conditions in a usually complex, multi-comorbid patient.

ALGORITHM

To our best knowledge, for this condition there is no validated treatment algorithm available in the literature. Following an exhaustive analysis of the available literature, we elaborated an algorithm for the diagnosis and treatment of HC (Fig. 2). The fulcrum of the diagnostics is the CT scan, which was used in most cases, and

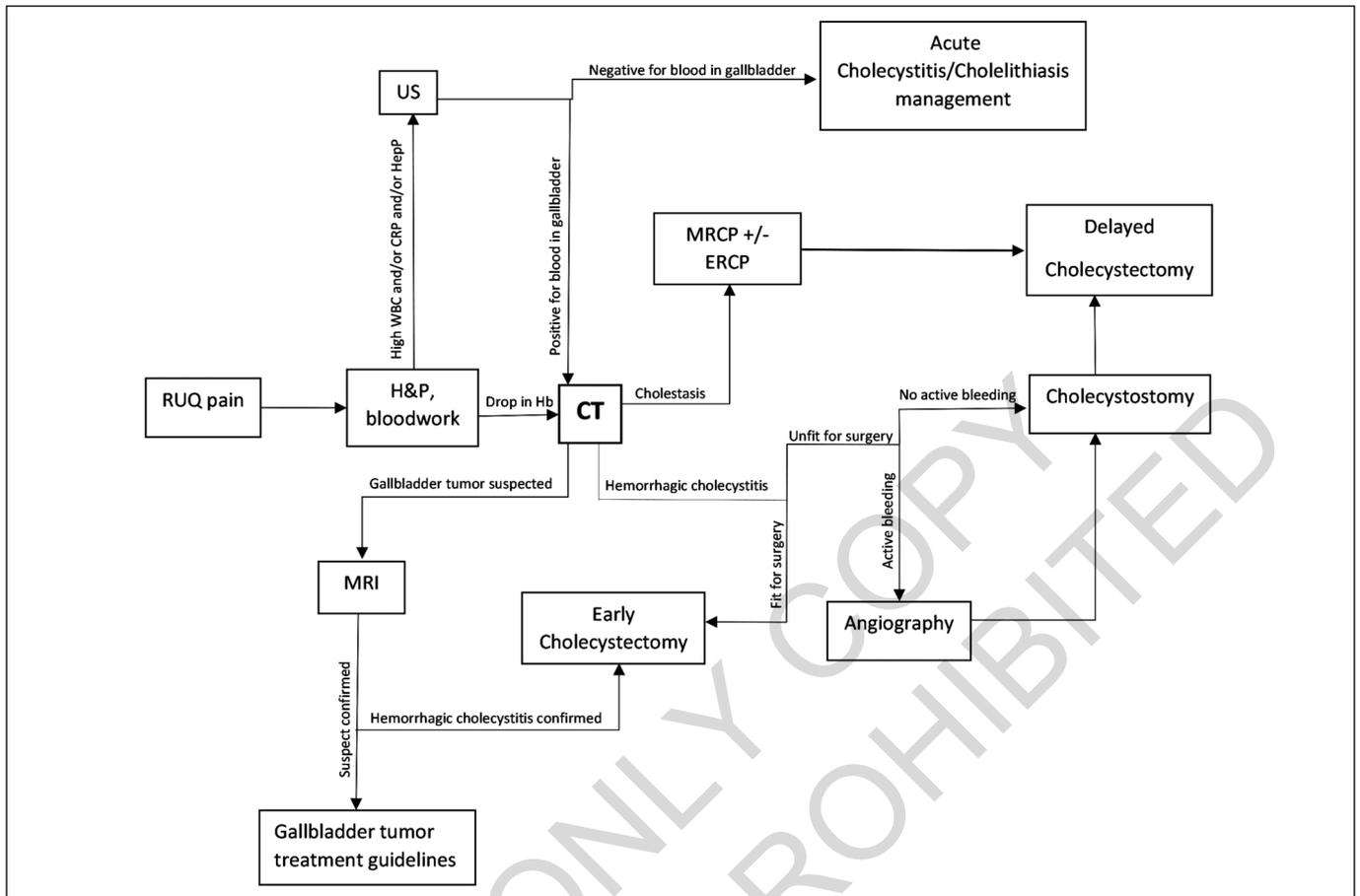


Fig. 2: HC treatment algorithm

(RUQ- right quadrant pain, H&P – history and physical examination, WBC – white blood cells, CRP – C-reactive protein, HepP – hepatic profile, CT – computer tomography, MRCP – magnetic resonance cholangiopancreatography, ERCP - Endoscopic Retrograde Cholangiopancreatography, MRI - magnetic resonance imaging).

should confirm or reject the diagnosis of HC. The subsequent treatment decisions are based on the patient's suitability for surgery. Unless cholestasis is present, good surgical candidates should undergo an early cholecystectomy. On the other hand, bad surgical candidates should be stabilized, should undergo angiography, if active bleeding is present, and eventually a cholecystostomy, as a bridge treatment for a delayed cholecystectomy.

Cholecystectomy is ultimately indicated in the vast majority of patients that can undergo surgery. A multidisciplinary perioperative approach may be helpful when treating, as seldom happens, a patient with numerous comorbidities. To date, most research available on HC consists of case reports. Further investigation is needed to clearly understand the pathogenesis of this condition in a tentative to define a comprehensive treatment algorithm.

Discussion and Conclusion

HC is a complication of AC that frequently affects patients with multiple comorbidities. The diagnosis of this pathologic entity is complex and should be well conducted in order to choose the correct treatment strategy. Ultrasonography and contrast-enhanced CT scan are the most used imaging modalities. When the diagnosis of HC is made, treatment must be started without hesitation. Treatment modalities vary substantially and depend on the severity of the condition and general patient's status with associated comorbidities.

Riassunto

La colecistite emorragica è una condizione rara che di solito costituisce una complicanza della colecistite acuta. La manifestazione clinica può essere multiforme e complessa con dolore addominale associato a febbre, ittero, nausea, vomito e, infine, emobilia. Spesso colpisce pazienti con preesistenti co-morbidità, quali insufficienza renale in trattamento dialitico o patologie in trattamento con anticoagulanti. Data la potenziale gravità di questa condizione una diagnosi ed un trattamento tempestivi sono essenziali per evitare un esito infausto. Al

fine di contribuire ad un miglioramento della sua strategia di trattamento in questo studio viene presentato un caso clinico, seguito da una revisione della letteratura. Nella banca dati Pubmed, con il termine “hemorrhagic cholecystitis” sono stati identificati 67 casi descritti nella letteratura di lingua inglese. I casi sono stati analizzati da due degli autori, quindi le informazioni cliniche sono state estrapolate e organizzate al fine di realizzare una revisione completa che possa essere chiara ed utile nella pratica clinica.

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